37. (Amended) A method according to Claim 35 wherein in step (a) at least one other SV40 protein, preferably SV40 agnoprotein, is added to the mixture of SV40 capsid protein or proteins and the exogenous antisense RNA or ribozyme RNA or RNA or DNA [nucleic acid or antisense nucleic acid].

41. (Amended) A mammalian cell infected with a complex [construct] of Claim 1.

42. (Amended) An infected [human] cell according to Claim 41, wherein the cell is a human cell selected from the group consisting of hemapoietic cells, muscle cells, tumor cells, nerve cells and germ line cells.

REMARKS

Claims 1-2, 4-13, 16-20, 22-37 and 41-46 are currently pending in the application. Claims 3, 14-15, 21 and 38-40 are cancelled. Claims 1-2, 4-13, 16-18, 20, 25, 27-29, 32, 35, 37 and 41-42 have been amended. The amendments and new claims find support in the specification, and are discussed in the relevant sections below. No new matter is added by these amendments.

Withdrawal of Rejection Under 35 U.S.C. § 102(b)

Applicants gratefully acknowledge the withdrawal of the rejection of Claims 18, 19, 21, 24, 29 and 30 under 35 U.S.C. § 102(b) in view of Forstova *et al.*

Withdrawal of Objection to the Specification

Applicants gratefully acknowledge the withdrawal of the objection to the specification.

Withdrawal of Rejection Under 35 U.S.C. § 112, First Paragraph

Applicants gratefully acknowledge the withdrawal of the rejection of Claims 1-17 under 35 U.S.C. § 112, first paragraph.

Withdrawal of Objection to Claims 1 and 18

Applicants gratefully acknowledge the withdrawal of the objection to Claims 1 and 18.

Clarification of Reasons for Withdrawal of Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of Claims 7, 10, 12, 25, 28 and 32 under 35 U.S.C. § 112, second paragraph, was withdrawn by the Examiner, the Examiner stating that, for the purposes of examination, the phrase "DNA which encodes as protein or peptide product wherein said protein or peptide product is not made or contained in said cell" is interpreted to mean that the protein of peptide encoded by the DNA of the construct is not made or contained in the cell at any time, including the time when the cell may contain the DNA construct. Applicants do not agree with the Examiner's reasons for withdrawal of the rejection.

Applicants note that interpretation of these claims as stated by the Examiner in the present Office Action is logically inconsistent. According to the Examiner's stated interpretation, the claimed constructs would contain exogenous nucleic acid that, when infected into cells that possess either no or defective or insufficient product, would produce cells containing the construct, yet *still* possessed either no or defective or insufficient product.

Notwithstanding the above, Applicants have amended Claims 7, 10, 12, 25, 28 and 32 to use the phrase "DNA which encodes a protein or peptide product wherein said protein or peptide product is not made or contained in said cell prior to infection with the construct". This amendment is supported by the specification and Examples, *e.g.*, page 13, line 3 discusses "...proteins which are missing... in patients suffering from genetic disorders." Applicants believe that the amended claims more clearly define the subject matter that Applicants regard as the invention.

Applicants therefore respectfully request that the Examiner withdraw the limitation that has been effectively placed on these claims in the reasons for the Examiner's withdrawal of the rejection.

Claim Objections

The Examiner has objected to Claim 1, stating that newly-entered claim limitations duplicate existing claim language at lines 4, 7, 10 and 12.

Applicants are making a diligent attempt to respond to the Office Action, but the claim objections made by the Examiner are unclear.

If the Examiner means that, *e.g.*, item (a) contains duplicate language because "exogenous DNA" seems to appear twice, this is not the case, because the exogenous DNA does

not necessarily have to encode a product, but can itself be a desired product, *e.g.*, for integration with existing cellular DNA.

On the other hand, if the Examiner means that the definitions "exogenous DNA encoding an exogenous protein or peptide product" (items (a) and (b)) and "exogenous RNA encoding an exogenous protein or peptide product" (items (c) and (d)) are duplicative, this is incorrect because in items (b) and (d) the exogenous constituent is a vector.

Applicants have amended Claim 1 to further clarify the subject matter of this claim, and therefore respectfully request that the objections to this claim be reconsidered and withdrawn.

The Examiner has also objected to Claim 6, stating that newly-entered claim limitations duplicate existing claim language at line 2.

Like the objections to Claim 1 above, Applicants are making a diligent attempt to respond to the Office Action, but the claim objection made by the Examiner is unclear. Applicants have therefore amended Claim 6 to further clarify the subject matter of this claim, and respectfully request that the objection to this claim be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 41, 42 and 46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in a such a way as to enable one of ordinary skill in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Specifically, the Examiner believes that the specification, "while being enabling for *in vitro* constructs, does not reasonably provide enablement for *in vivo* therapeutic use for the construct." The Examiner than states that "[t]he claims are drawn to a construct of SV40 viruses or pseudoviruses" in which "the exogenous nucleic acid or [an] exogenous protein is therapeutic" and to "therapeutic methods of using the construct."

This is not correct. Claims 41 and 42 are drawn to cells infected with the constructs, and Claim 46 is drawn to compositions comprising the infected cells. No *in vivo* or therapeutic use is recited in Claims 41, 42 and 46. Applicants have fully enabled constructs and construct-infected cells as claimed. Applicants therefore respectfully request that the rejection of these claims on this basis be reconsidered and withdrawn.

Claims 43 and 44 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in a such a way as to enable one of ordinary skill in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner believes that these claims are drawn to "therapeutic methods of using the construct of using the construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid", and that undue experimentation is required.

In response to the previous Office Action, Applicants had amended these claims to remove any reference to therapy. Even so, the Examiner now reiterates the same rejection to these same claims as stated in the previous Office Action, and has not altered the interpretation of these claims. Because the Examiner's rejection is based on language that is no longer present in these claims, Applicants respectfully request that the rejections on this basis be reconsidered and withdrawn.

Claims 1-46 are also rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Specifically, the Examiner believes that the specification, "while being enabling for SV40 capsid formation using VP1 alone, does not reasonably provide enablement for SV40 capsid formation using VP2 or VP3 alone" and that "[e]ither VP1 or VP1 in combination with VP2 and VP3 are the only enabled embodiments."

Applicants have amended Claims 1-2, 4-13, 16-18, 20, 25, 27-29, 32, 35, 37 and 41-42 and cancelled claims 3, 14-15, 21 and 38-40. Applicants respectfully request that the rejection to Claims 1-46 on this basis be reconsidered and withdrawn.

Claims 1-17 and 35-46 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants have canceled claims 3, 14-15 and 38-40, and the rejection as against these claims is therefore moot.

With regard to Claims 1-4, 6-13, 16-17, 35-37 and 41-46, the Examiner reiterates the rejections of the previous Office Action, stating the belief that the "specification does not sufficiently describe the possible inventions drawn from the claims", and that "[t]here is no

information given regarding the structures of a gene that may suggest potential antisense oligonucleotides which may be created or found."

In reponse to Applicants' prior-filed arguments, the Examiner asserts that "the prior art taught at the time of filing of the instant application[,] that an antisense molecule could not be predicted from a large tract of DNA" and that "the only way to identify the active region of a large tract was by trial and error".

Applicants respectfully disagree. The Examiner's argument is largely baseless. The present invention describes constructs that are used to deliver a number of different types of nucleic acid molecules, including antisense molecules. Applicants are providing a construct that can be used by the person needing a delivery system for an antisense molecule. Applicants' invention is therefore a tool, *e.g.*, a delivery vehicle, which Applicants have recognized to be useful to those practicing in other fields, including the field of antisense therapy. Under the Examiner's reasoning, there would be no allowed inventions in the field of hypodermic needles, on the grounds that development of pharmaceuticals and vaccines requires undue experimentation.

Applicants therefore respectfully request that the rejection of these claims on this basis be reconsidered and withdrawn.

Claims 1-8, 10-26 and 8-46 are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Specifically, the Examiner's reasoning consists of the belief that the specification states at pages 19 and 20 that an *ori* sequence is necessary, and that since claims 9 and 27 recite sequences comprising *ori*, that the remaining claims do not require *ori*, and are therefore not enabled.

Lines 23-25 of page 20 of the specification, upon which the Examiner appears to rely for this argument, clearly state that "[i]n the present examples, the *ori* element was required for **the assay** of infectious units" (emphasis added), not **the packaging** of infectious units.

In addition, page 5, line 13-16, and page 13, lines 6-7 of the specification state that the constructs of the present invention "*may* comprise SV40-derived *ori* DNA sequence" (emphasis added). Page 20, lines 19-27 of the specification do state that the *ori* sequence was present, but it is also stated that constructs without *ori* are contemplated by the invention (page 20, lines 22-23).

The plasmids used in the examples included SV40 *ori* because the *ori* was required for the particular assay for *in vitro* packaging that was used in the example, and not for the packaging reaction proper.

The assay used in the example measured infectious units as infective centers. As described, the test cells were CMT4 monolayers that are susceptible to SV40 infection. These cells were engineered to harbor the SV40 T-antigen gene, expressed from the metallothionein promoter, which is inducible by heavy metals (Zn and Cd). Following infection with the products of the *in vitro* packaging reaction, the CMT4 monolayers were treated with heavy metals (Zn and Cd) in order to induce the endogenous SV40 T-antigen gene. This allowed the *in vitro* packaged plasmid, containing the SV40 *ori*, to replicate extensively in the CMT4 cells and to produce a signal as an "infective center". The assay for infective centers is performed two days later, as follows: the monolayers are transferred onto a nylon membrane, treated with sodium hydroxide to open the cells and melt the DNA, and then hybridized with a probe specific for the plasmid used in the packaging reaction. Each cell that was infected becomes an "infection center", producing a radioactive signal visible on X-ray film after appropriate exposure (see Fig. 2a). The resulting dots are then counted and used to calculate the efficiency of the particular packaging reaction. The DNA replication of the plasmid DNA is essential in order to amplify the signal obtained from each infective center so that it will be visible for counting in the assay. This DNA replication and signal amplification is facilitated by the SV40 *ori* in the packaged plasmid, and is driven by the T-antigen provided by the CMT4 cells. Thus, the SV40 *ori* is needed for the infective centers to appear in the assay, and not for packaging *per se*.

This assay was convenient for the development of the system because it is applicable, with no modification, to any plasmid. The only requirement *for this specific assay*, is that the plasmid contains the SV40 *ori*. This by no means implies that the *ori* element is required for the packaging, as detailed above. Applicants have produced constructs according to the invention that are devoid of *ori*, and the constructs are capable of infecting cells effectively. These data can be provided in the form of a Declaration upon request by the Examiner.

Applicants therefore respectfully request reconsideration and withdrawal of the rejection on this basis.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-17, 20, 25 and 27-46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner states that use of the phrase "capable of" renders Claim 1 indefinite, and reiterates arguments from the previous Office Action. Applicants disagree, and maintain the arguments against this rejection that were put forth in the reply to the previous Office Action. Nevertheless, in the interests of advancing prosecution, Applicants have amended Claim 1 to remove this language. Applicants therefore request that the rejection on this basis be withdrawn.

The Examiner also states that Claim 1 is indefinite, stating that the phrase "exogenous protein" in line 26 of this claim lacks antecedent basis. Applicants have studied this claim carefully, and find that Claim 1 is only 20 lines long. "Exogenous protein" does occur in line 26 of page 2 of the Reply to the previous Office Action, but this is in a section of text that has been deleted. Applicants request that the Examiner clarify, or withdraw the rejection.

The Examiner also rejected Claim 1, stating that there is an internal inconsistency in that part e) states that the constituent is a protein or peptide, while the preamble recites a DNA construct. Applicants have amended the preamble to recite a "complex". Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner also rejected Claim 1, stating that the DNA construct comprises a protein. Applicants have followed the Examiner's suggestion, and have amended the preamble to recite a "complex". Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner also rejected Claims 1, stating that the phrase "an RNA ... or itself a protein or peptide product" is unclear. Applicants have amended this claim to remove this language, and respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner also rejected Claim 1, stating that an origin of replication is not an art-recognized regulatory element. Applicants have amended this claim to delete "regulatory", and respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner rejected Claim 6, stating that use of the term "vector" is unclear. Applicants have deleted this language, and respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner rejected Claims 7, 10, 12, 25, 28 and 32, stating that the phrases "abnormally low amount", "normal amount", and "defective form" are unclear. Applicants disagree, and maintain, as discussed in the Reply to the previous Office Action, that one of ordinary skill in the art would know or be able to determine what constituted "abnormally low amount", "normal amount", and "defective form". Nevertheless, Applicants have amended these claims to recite "an amount insufficient for proper cell function" instead of "abnormally low amount", to recite "a form inadequate for proper cell function" rather than "defective form", and have deleted "normal amount" altogether. If these amendments are not acceptable, Applicants are willing to consider suggestions from the Examiner regarding acceptable alternative language. In light of the present amendments, Applicants respectfully request that the rejection of these claims on this basis be reconsidered and withdrawn.

The Examiner stated that the use of the phrase "liver cells" is inconsistent in Claims 16 and 17. Applicants have deleted this phrase from Claim 17, and respectfully request that the rejection on this basis be reconsidered and withdrawn.

The Examiner has rejected Claim 20, stating that there is lack of antecedent basis for the term "said nucleic acid". This is incorrect, as this claim depends from Claim 18, which recites the phrase "said nucleic acid". However, Applicants have amended this claim to recite "said exogenous nucleic acid" in order to more clearly set out the antecedent basis. Applicants therefore respectfully request that the rejection of this claim on this basis be reconsidered and withdrawn.

The Examiner has rejected Claim 27, stating that there is insufficient antecedent basis for the phrase "said cell." Applicants have amended this claim, and respectfully request that the rejection of this claim on this basis be reconsidered and withdrawn.

The Examiner has rejected Claim 30, stating that there is insufficient antecedent basis for the phrase "said cell." This phrase does not occur in this claim, and Applicants therefore respectfully request clarification, or that the rejection of this claim on this basis be reconsidered and withdrawn.

The Examiner has rejected Claim 32, stating that there is insufficient antecedent basis for the phrase "said cell." Applicants have amended this to "a cell", and respectfully request that the rejection of this claims on this basis be reconsidered and withdrawn.

The Examiner has rejected Claim 33, stating that there is insufficient antecedent basis for the phrase "said cell." Applicants have amended Claim 32. Claim 33, which depends from

Claim 32, now have sufficient antecedent basis. Applicants respectfully request that the rejection of this claim on this basis be reconsidered and withdrawn.

The Examiner rejected Claim 37, stating that there is insufficient antecedent basis for the phrase "exogenous nucleic acid". Applicants have amended this claim, and respectfully request that the rejection of this claim on this basis be reconsidered and withdrawn.

The Examiner rejected Claim 42, stating that there is insufficient antecedent basis for the phrase "human cell." Applicants have amended this claim, and respectfully request that the rejection of this claim on this basis be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 102(b)

Rejection in View of Christansen et al.

Claims 1-7, 9-10, 12, 16-25, 27-34 and 41-42 are rejected under 35 U.S.C. § 102(b) as anticipated by Christiansen *et al.* (*Virology* 75:433-441, 1976), the Examiner maintaining the reasons stated in the prior Office Action. The Examiner believes that Christiansen *et al.* teach pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses.

Applicants respectfully disagrees. Christensen *et al.* do not teach a method of construction of viruses and pseudoviruses. They report the recovery of infectious aggregates, and these aggregates are not physically identical to SV40 virions (page 433, end of Introduction).

They did not use "SV40 capsid proteins and at least one other SV40 protein" as mistakenly indicated by the Examiner. They used SV40 capsids, which contain SV40 VP1, VP2 and VP3, and instead of the exogenous constituent defined in present Claim 1, SV40 nucleoprotein (NP) complex, which contains SV40 DNA and cellular histones. Thus they have not used any "other SV40 protein". Instead they have used SV40 capsids and the histone proteins within the nucleoprotein complex, which are additional cellular proteins. This absence of histones is referred to in the present application (page 33, last lines).

A key element in Christensen *et al.* is the use of nucleoprotein complexes, *i.e.*, the DNA is complexed with histones in nucleosomes. The present invention describes the packaging of naked DNA, without histones. This is a major difference. The absence of histones renders the constructs of the invention novel over Christensen *et al.*

Nucleoprotein (NP) complexes are not DNA. These complexes have completely different properties. The histones condense the DNA that they associate with. Thus NP complexes possess different physical characteristics from DNA. They can be separated from DNA by a variety of biophysical methods, *i.e.*, centrifugation, electrophoresis, gradient sedimentation, proving that they have different qualities.

Because of their different biophysical properties, the natural interaction between SV40 capsids and NP complexes is very different from the interaction between capsids and pure naked DNA. Therefore, the method taught by Christensen *et al.*, of interacting NP with empty SV40 capsids, does not anticipate the packaging of naked DNA demonstrated by the present invention, in the absence of histone proteins. The resulting constructs are also different.

Importantly, histones, when complexed with DNA to form NP, substantially enhance the efficiency of delivery of the DNA into mammalian cells grown in tissue culture, proving that NP are different from naked DNA. Histones are used in many gene therapy development programs as a "nonviral vector", with efficiency of gene delivery comparable to or better than that of liposomes. Therefore, the packaging of histone-containing NP in empty SV40 shells is also completely different from the packaging of naked DNA. As packaging of naked DNA requires different conditions from packaging of NP complexes, Christensen *et al.* did not teach the packaging of naked DNA.

The exclusion of histones facilitates packaging of plasmids which are significantly larger than the SV40 genome, and the inclusion of potency regulatory signals. The present invention facilitates packaging of plasmids of 7-7.4 kb (see Table 3, page 33). The space within an SV40 particle limits the packaging size of a nucleoprotein complex to about 5.4 kb (Martin, R.G., *Virology* 83:433-447, 1997 (reference AR5 of Information Disclosure Statement); Chang, X.B. and Wilson, J.H., *J. Virol.* 58:393-401, 1986 (reference AY4 of Information Disclosure Statement)). In fact, the demonstration by Applicants of the packaging of much larger plasmids, even without more, shows the difference between the constructs of of the present invention and those of Christensen *et al.*, because with the constructs of Christensen *et al.* it would not have been possible to package a nucleoprotein complex of a size exceeding about 5.4 kb. Christensen *et al.*, being aware of this limitation, allowed their capsids to be complexed with SV40 nucleoprotein, which contains 5.2 kb of DNA. Only because naked DNA is packaged, is it possible to package the very large plasmids shown in Table 3 of the present invention.

The exclusion of histones also allows packaging of potent regulatory elements, such as the β-globin locus control region (LCR). As shown in Table 3 of the application, β-globin LCR elements do not adversely affect the efficiency of packaging of naked DNA. In contrast, these elements cause great problems in packaging of nucleoprotein complexes, due to the formation of higher order structures that are not compatible with the nucleosomal condensation, which is required for packaging (Dalyot, N., Ph.D. Thesis, 1994 (reference AZ4 of Information Disclosure Statement)). The ability to package naked DNA that carries the β-globin LCR demonstrates the difference between the constructs of Christensen *et al.* and those of the present invention, because it is not possible to package a nucleoprotein complex that contains the β-globin LCR.

It should be appreciated that preparing vectors without histones, as in the present application, simplified the packing reaction. Taking a DNA plasmid and decorating it with histones requires a number of additional steps. Moreover, obtaining human histone proteins is not trivial.

From all of the above it is clear that the method taught by Christensen *et al.*, of complexing NP with empty SV40 capsids, does not anticipate the packaging of naked DNA in the absence of histone proteins demonstrated by the present invention, and reconsideration and withdrawal of the rejection is respectfully requested.

Rejection in View of Colomar et al.

Claims 1-8, 9-10, 12, 16-25, 27-34 and 41-42 were rejected under 35 U.S.C. § 102(b) as anticipated by Colomar *et al.* (*J. Virol.* 67:2779-2788, 1993). The Examiner believes that Colomar *et al.* teach a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. Applicants respectfully disagree.

Colomar *et al.* do not teach a method of construction of viruses and pseudoviruses. They teach the disruption and refolding of SV40 into compact infectious particles. In their experiments, they subjected SV40 virions to conditions of dissociation and then reassociated the capsids with the original nucleoprotein complexes by changing the composition of the buffer. The capsid proteins and the nucleoprotein complexes were never fully separated from each other. Their results showed in Fig. 4a and 4b that at least some of the capsid proteins remained in

association with the DNA at all times. Even under these mild dissociation-reassociation conditions infectivity of the virus was decreased 10,000 fold (Table 1).

The experiments of Colomar *et al.* showed that "the reassembled particles were imperfect", and they suggest that their reassembly method "selected for viral DNA molecules which were shorter than full length" (page 2785, 3rd paragraph). This is in contrast to DNA or other exogenous constituents packaged in SV40 capsids as claimed in the present invention. DNA packaged as in the present invention is identical in size to the input DNA (Fig. 3b in Sandalon *et al., Hum. Gene Ther.* 8:843-849, 1997 (reference AU3 in the Information Disclosure Statement). There is no selection of any molecules of different size.

Colomar *et al.* did not use "SV40 protein and at least one other SV40 protein" as mistakenly indicated by the Examiner. They used disrupted SV40 capsids, which contain SV40 VP1, VP2 and VP3, and SV40 nucleoprotein (NP) complex which were originally in the same capsids, which contains SV40 DNA and cellular histones. Thus they have not used any other SV40 protein. Instead they have used SV40 capsids and the histone proteins in the nucleoprotein complex, which are additional cellular proteins. The constructs described in Colomar *et al.* are thus structurally different from the claimed complex constructs.

From all of the above it is clear that Colomar *et al.* did not teach the packaging of heterologous DNA to form functional infective virus or pseudovirus, and reconsideration and withdrawal of the rejection on the basis of this reference is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Rejection in View of Christensen et al. or Colomar et al., in View of Carswell et al., Oppenheim et al. and U.S. Patent No. 5,863,541

Claims 1-13, 15-37 and 39-46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Christensen *et al.* or Colomar *et al.*, in view of Carswell *et al.* (*J. Virol.* 60:1055-1061, 1986), Oppenheim *et al.* (*Proc. Natl. Acad. Sci. USA* 83:6925-6929, 1986) and U.S. Patent No. 5,863,541. Specifically, the Examiner believes that either Christiansen *et al.* or Colomar *et al.* teach the present invention, and the combination of these references renders obvious Applicants' invention.

As stated above, neither Christensen *et al.* nor Colomar *et al.* anticipate Applicants' invention, and combining either or both of these references with Carswell *et al.* and Oppenheim

et al. fails to render obvious Applicants' invention. Applicants maintain the arguments presented in the Reply to the previous Office Action.

In rebuttal to that Reply, the Examiner stated in the present Office Action that "one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references." While this may be true, it is also true that Applicants are required under 37 C.F.R. § 1.111 to "distinctly and specifically ... reply to every ground of objection and rejection in the prior Office action." The "reply must appear throughout to be a bona fide attempt to advance the application or the reexamination proceeding to final action."

The Examiner has failed to make out a *prima facie* case of obviousness. The Manual of Patent Examining Procedure states at § 2142 that

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

(citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), and that

> The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references."

(citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)).

In the Reply to the previous Office Action, Applicants explained their reasoning as to why Christensen *et al.* and Colomar *et al.* fail to either anticipate or render obvious Applicants' invention, either alone or in combination with other references. In the present Office Action, the Examiner has nevertheless maintained the rejection, stating that Christensen *et al.* teach " a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses." As stated in the Reply to the previous Office Action, Christensen *et al.* do not describe the packaging of SV40 psuedovirions, but teach the disruption of SV40 virions and the formation of infectious DNA protein aggregates,

which consist of SV40 proteins and nucleoprotein complexes. Applicants' invention on the other hand describes the packaging of naked, heterologous, supercoiled DNA. Applicants therefore respectfully request that the Examiner clearly explain why the rejection is maintained in view of the Christensen *et al.* reference.

The Examiner has also maintained the rejection based on U.S. Pat. No. 5,863,541, stating that one of ordinary skill would be motivated to modify the method of Christensen *et al.* or Colomar *et al.* with the method of U.S. Pat. No. 5,863,541, Carswell *et al.* or Oppenheim *et al.*, because U.S. Pat. No. 5,863,541 states at column 3, lines 11-13 that other molecules (*e.g.*, DNA, RNA, proteins, etc.) can be used with the method of U.S. Pat. No. 5,863,541 and that the method may be particularly advantageous in AAV gene delivery systems. However, Applicants pointed out in the Reply to the previous Office Action that AAV and SV40 have many differences, including belonging to different viral Classes and having very different levels of autonomy. The Examiner has not rebutted Applicants' statements, but has instead simply stated that Applicants cannot attack the references individually and that the references teach "well known and advantageous methods." The Examiner has provided no basis for the assumption stated on page 17 of the present Office Action that these viruses are equivalent for the delivery of exogenous nucleic acids. Applicants maintain the arguments presented in the Reply to the previous Office Action, and respectfully request that the Examiner clearly explain why the rejection is maintained in view of U.S. Pat. No. 5,863,541.

The MPEP states at § 2142 that the "teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure", and that in making a determination of non-obviousness,

> Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

In the Reply to the previous Office Action, Applicants responded to the Examiner's characterization of Christensen *et al.*, Carswell *et al.*, Oppenheim *et al.* and U.S. Pat. No. 5,863,541, and have responded above regarding Colomar *et al.* In the present Office Action, the Examiner has stated that it would have been obvious to modify the method of Christensen *et al.* or Colomar *et al.* with the methods of the other three references to produce the instant invention,

"because the capsid proteins of US Pat No. 5,863,541 *were assembled in a like manner to the instant claimed invention*, and inclusion of nucleic acids which encode various therapeutic entities *is an obvious extension* of the gene therapy teachings of Christensen et al. or Colomar et al." (emphasis added). Applicants believe that the Examiner is using the Applicants' invention as a blueprint to assemble the cited references. This is impermissible. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability -- the essence of hindsight." *In re Dembiczak* (50 USPQ2d 1614 (Fed. Cir. 1999)).

The Examiner has not pointed to any specific passages in the cited references which provide motivation to combine those references, nor to any other sources for such motivation. Rather, the Examiner relies on statements that "it would have been obvious . . . to modify the method" of the references to produce Applicants' invention, that portions of Applicants' invention "is an extension" of the methods of a reference, that "it is assumed" that the making of AAV pseudovirions and SV40 virions "is equivalent" for the purpose of delivering exogenous nucleic acids and proteins to cells, that the references "merely taught well known and advantageous methods" of facilitating the assembly of SV40 capsid proteins into SV40 capsids, or that the references are "justifiably combined" because they are "used to demonstrate well known and obvious elements which are used to study related subject matter". The Examiner has not stated with any specificity why one of ordinary skill in the art at the time the invention was made would be motivated to combine the cited references and passages therein to produce Applicants' invention.

The MPEP states that

> There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). *The level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

§ 2142 (emphasis added), and that

> In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the

> reference before him to make the proposed substitution, combination, or other modification.

Citing *In re Linter* (458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972)). The Examiner must therefore state *why* one of ordinary skill would be motivated to combine the references, *e.g.*, from the references themselves, from the knowledge of one of ordinary skill, or the nature of the problem to be solved. "[T]he references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious" (*Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985)).

The fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness ("The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP § 2142, citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). In addition, the fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness:

> A statement that modifications of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.

MPEP § 2142, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

The Examiner has failed to provide motivation for the combining of the references, and has also failed to establish that the cited references disclose Applicants' invention. A *prima facie* case of obviousness has therefore not been made. Applicants respectfully request that that the rejection under 35 U.S.C. § 103(b) be reconsidered and withdrawn.

Rejection in View of Christensen et al. or Colomar et al., in View of Carswell et al., Oppenheim et al., U.S. Patent No. 5,863,541 and Szczylik et al.

Claims 14 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Christensen *et al.* or Colomar *et al.*, in view of Carswell *et al.* (*J. Virol.* 60:1055-1061, 1986), Oppenheim *et al.* (*Proc. Natl. Acad. Sci. USA* 83:6925-6929, 1986), U.S. Patent No. 5,863,541 and Szczylik *et al.* (*Science* 253:562-565, 1991). Specifically, the Examiner believes that either

Christiansen *et al.* or Colomar *et al.* teaches the present invention, and the combination of these references renders obvious Applicants' invention.

Applicants have addressed Christensen *et al.*, Colomar *et al.*, Carswell *et al.*, Oppenheim *et al.* and U.S. Patent No. 5,863,541 above. The Examiner has failed to establish a *prima facie* case of obviousness with regard to these references, and the addition of Szczylik et al. does not make up the deficiencies of these references.

Applicants have cancelled Claims 14 and 38. The rejection is therefore moot.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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